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SYSTEMATIC REVIEWS

How Should We Deal with Patient Heterogeneity in Economic Evaluation: A Systematic Review of National Pharmacoeconomic Guidelines

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ABSTRACT

Objective: To review and analyze recommendations from national pharmacoeconomic guidelines with regard to acknowledging patient heterogeneity in economic evaluations. **Methods:** National pharmacoeconomic guidelines were obtained through the ISPOR Web site. Guidance was extracted by using a developed data extraction sheet. Extracted data were divided into subcategories on the basis of consensus meetings. **Results:** Of the 26 included guidelines, 20 (77%) advised to identify patient heterogeneity. Most guidelines (77%) provided general methodological advice to acknowledge patient heterogeneity, including justifications for distinguishing subgroups (65%), prespecification of subgroups (42%), or methodology to acknowledge patient heterogeneity (77%). Stratified analysis of cost-effectiveness was most commonly advised (20 guidelines; 77%); however, guidance on the specific application of methods was scarce (9 guidelines; 34%) and generally limited if provided. Guidance to present patient heterogeneity was provided by 15 guidelines (58%), most prominently to describe the definition (31%) and justification (31%) of subgroups. **Conclusions:** The majority of national pharmacoeconomic guidelines provide guidance on acknowledging patient heterogeneity in economic evaluations. However, because guidance is mostly not specific, its usefulness is limited. This may reflect that the importance of acknowledging patient heterogeneity is usually recognized while there is a lack of consensus on specific methods to acknowledge patient heterogeneity. We advise the further development of national pharmacoeconomic guidelines to provide specific guidance on the identification of patient heterogeneity, methods to acknowledge it, and presenting the results. We present a checklist that can assist in formulating these recommendations. This could facilitate the systematic and transparent handling of patient heterogeneity in economic evaluations worldwide.

Keywords: economic evaluation, national pharmacoeconomic guideline, patient heterogeneity, systematic review.

Introduction

Considering the rapidly increasing health care costs and the finite amount of available resources, the criteria to grant reimbursement to new treatments have become more restricted. These reimbursement decisions are often made for groups of patients. A more individualized approach for the allocation of available resources, that is, providing treatment reimbursement for subgroups of patients, however, has the potential to increase population health gains [1–4]. Acknowledging patient heterogeneity in reimbursement decisions may lead to more efficient health care if these reimbursement decisions are based on cost-effectiveness [5]. As economic evaluations are frequently used to estimate cost-effectiveness and support reimbursement decision making [6], it is essential that patient heterogeneity be incorporated in economic evaluations. Although there is consensus on its importance [7], patient heterogeneity is frequently neglected in economic evaluations [8].

Patient heterogeneity might be neglected because subgroup policy sometimes is controversial due to ethical concerns. This may lead to equity constraints, where the use of certain characteristics is considered unacceptable to determine which subgroups have access to a technology. The acknowledgment of patient heterogeneity in economic evaluations also seems to be hampered by a lack of clarity on when and how this should be done [2,9]. In this respect, there is an important role for national pharmacoeconomic guidelines. National pharmacoeconomic guidelines provide essential guidance how economic evaluations, with the purpose to support reimbursements decision making, should be performed within a jurisdiction. The objective of this study was therefore to review and analyze recommendations from national pharmacoeconomic guidelines with

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regard to acknowledging patient heterogeneity in economic evaluations.

Methods

Definition of Patient Heterogeneity

Patient heterogeneity was defined as the part of the natural variation between patients (variability) that can be attributed to characteristics of those patients [6,9,10]. This was differentiated from treatment variability (differences in the nature of the treatment), differences between geographical regions that may impact cost-effectiveness, and statistical heterogeneity. These concepts relate more to the generalizability of cost-effectiveness results [9,11] and variation in outcomes between studies (e.g., included in a meta-analysis) and are beyond the scope of this review.

Characteristics that potentially explain patient heterogeneity include demographics (e.g., age, sex, and income), preferences (e.g., attitude, beliefs, and risk tolerance), and/or clinical characteristics (e.g., disease severity, disease history, and genetic profile) [9]. These sources of patient heterogeneity may have an impact on different input parameters used in an economic evaluation: baseline risks, relative treatment effects, health state utility, and resource utilization [9]. Differences in unit costs are more likely a result of differences between geographical regions and are thus not considered in this review [9,12].

Search Strategy and Data Extraction

Consistent with previous reviews of national pharmacoeconomic guidelines [12,13], national pharmacoeconomic guidelines were obtained through the link provided on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Web site (www.ispor.org) [14] and retrieved from the Web site of the guideline agencies. This was done to ensure that the most recent versions were retrieved. The ISPOR Web site was considered a reliable and valid source because the overview of national pharmacoeconomic guidelines is based on contacts with experts from approximately 60 countries from around the world [12]. Guidelines were included if they were available in English. To systematically extract relevant guidance, we used a data extraction sheet (see Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.02.013) containing the following categories:

1. Acknowledgment of patient heterogeneity: whether guidelines advised to identify patient heterogeneity and whether a distinction is made between different inputs of an economic evaluation: 1) baseline risk, 2) relative treatment effect, 3) health state utility, and 4) resource utilization.
2. Methodology to acknowledge patient heterogeneity: whether guidelines advised methodology to acknowledge patient heterogeneity. This contains guidance whether to justify for acknowledging patient heterogeneity (including equity constraints), guidance whether to a priori prespecify potential sources of patient heterogeneity, general methods, and the specific application of methods to acknowledge patient heterogeneity.
3. Presentation of patient heterogeneity: whether guidelines advised what should be presented when acknowledging patient heterogeneity.

Data were extracted and categorized (into the above-mentioned categories) by one author (B.R.). Extracted data from all guidelines were divided into subcategories. If the classification of guidance was ambiguous, it was independently judged by the other authors (J.G. and M.J.). Possible discrepancies were discussed to reach consensus.

Results

In total 33 guidelines were retrieved. Seven guidelines were excluded because they were not available in English [15–21]. This accumulated to 26 included guidelines, published between 1997 and 2012 [22–47].

Acknowledgment of Patient Heterogeneity

Most guidelines (20; 77%) advise to identify patient heterogeneity in general [22–41]. Thirteen guidelines (50%) explicitly consider it relevant to identify the impact of patient heterogeneity on effects in general (irrespective of whether it has an impact on the baseline risk and/or treatment effect) [22–25,27,29,30,32,34–36,38,40]. Seven guidelines (27%) specify this into differences in baseline risk and treatment effect and consider them both as relevant [22–25,30,32,36]. In addition, four guidelines consider it relevant to reflect the impact of patient heterogeneity on health state utility [24,27,30,34]. Nine guidelines (35%) consider differences in resource utilization as relevant input to acknowledge patient heterogeneity [23–25,29,30,34,36,38,40]. None of the guidelines advise not to identify patient heterogeneity in any of these four key inputs of an economic evaluation.

Methodology to Acknowledge Patient Heterogeneity in Economic Evaluations

Methodological guidance on acknowledging patient heterogeneity is provided by 20 guidelines (77%) [22–41].

Arguments to justify acknowledging patient heterogeneity in economic evaluations

Arguments to justify acknowledging patient heterogeneity are required by 17 guidelines (65%) [22–27,29,30,32–37,39–41]. Only the England & Wales guideline [25] lists equity constraints (Table 1). Instead of neglecting subgroups based on a particular equity point of view, the Canadian guideline [24] proposes to calculate the opportunity costs of equity concerns by using the framework proposed by Coyle et al. [1]. These opportunity costs can be interpreted as the costs of neglecting subgroups based on grounds of equity. Hence, this framework aims to inform the trade-off between equity and efficiency [1]. In addition, the German guideline states that only those subgroups should be addressed for which an additional benefit or lesser harm was established [28].

Specification of potential sources of patient heterogeneity

Eight guidelines (31%) [22,24,25,29,30,32,35,37] advise to prespecify potential sources of patient heterogeneity (Table 1). The French guideline considers post hoc multivariate analysis acceptable to explore patient heterogeneity [27]. Post hoc analysis is allowed under certain conditions by eight guidelines (31%): only for differences in costs [23], with (strong) justification [24,36] and/or if interpreted as explorative [23], with caution [22,30,32], or hypothesis generating [24,35].

How to acknowledge patient heterogeneity

Most guidelines (20; 77%) provide general advice how to acknowledge patient heterogeneity [22–41]. Stratified analysis is the most commonly advised method [22–41]. The French, German, and Scottish guidelines generally advise the use of decision analytic modeling [27,28,36]. Furthermore, sensitivity and/or scenario analyses are advised by the guidelines from Australia, Canada, and England & Wales [22,24,25]. Although most guidelines

Table 1 – Overview of advice on methodology from guidelines (N = 26) to acknowledge patient heterogeneity.

	Guidelines, n (%)		Countries
Total	20 (77)		AU, BC, BE, CA, EW, FI, FR, DE, HU, IE, IT, NZ, NO, PL, PT, SL, ZA, ES, SE, US
A Guidelines that advised to justify for acknowledging patient heterogeneity	17 (65)		AU, BC, BE, CA, EW, FI, FR, HU, IE, NZ, NO, PL, PT, SL, ZA, SE, US
Specific guidance:			
• If plausible based on (pre)clinical evidence/ pharmacokinetics		11 (42)	AU, BC, BE, EW, FR, HU, IE, NZ, PT, ZA, US
• If plausible based on a priori expectations of cost-effectiveness		7 (27)	BC, BE, EW, HU, IE, SE, US
• If biologically plausible		5 (19)	AU, EW, IE, NZ, SL
• If statistically plausible		4 (15)	AU, FR, NZ, ZA
• If patients for whom it is most (cost-) effective can be targeted/if relevant for decision		4 (15)	NZ, NO, ZA, US
• If relevant for distributive aspects/if patient groups likely to be disadvantaged can be targeted		2 (8)	CA, FR
• If informative for value-based pricing		1 (4)	FI
• If subgroups are within the approved indication		1 (4)	ZA
• If not solely based on: 1) individual utilities for health states and patient preferences, or 2) differential treatment costs for individuals according to their social characteristics		1 (4)	EW
B Guidelines that advised to prespecify potential sources of patient heterogeneity	11 (42)		AU, BE, CA, EW, FR, HU, IE, NZ, PT, SL, ZA
Specific guidance:			
• Prespecify subgroups		8 (31)	AU, CA, EW, HU, IE, NZ, PT, ZA
• Interpret post hoc analysis as explorative/as hypothesis generating/with caution		6 (23)	AU, BE, CA, IE, NZ, PT
• Ad hoc data mining should be avoided		3 (12)	BE, EW, SL
• Post hoc analysis is allowed only with (strong) justification		2 (8)	CA, SL
• Post hoc analysis only for differences in costs		1 (4)	BE
• Post hoc multivariate analysis is acceptable to explore patient heterogeneity		1 (4)	FR
C Guidelines that advised how to acknowledge patient heterogeneity in economic evaluations	20 (77)		AU, BC, BE, CA, EW, FI, FR, DE, HU, IE, IT, NZ, NO, PL, PT, SL, ZA, ES, SE, US
Suggested methods:			
• Stratified analysis		20 (77)	AU, BC, BE, CA, EW, FI, FR, DE, HU, IE, IT, NZ, NO, PL, PT, SL, ZA, ES, SE, US
• Decision analytic modeling		3 (12)	FR, DE, SL
• Sensitivity analysis/scenario analysis		3 (12)	AU, CA, EW
Specific advice on the application of methods:			
• Statistical precision of subgroups estimates should be reflected in the analysis of parameter uncertainty		3 (12)	CA, EW, SL
• Calculate the impact of variability in baseline risk by multiplying the expected baseline risk across patient subgroups by the overall relative treatment effect (established in the whole population)		3 (12)	AU, BE, NZ
• Meta-regression to determine whether a treatment effect varies across patient groups		2 (8)	AU, SL
• Calculate the impact of variability in absolute treatment effect by applying the estimated relative treatment effect for the subgroups to the expected baseline risk for the subgroups		1 (4)	AU
• Discrete event simulation		1 (4)	DE
• Sensitivity analysis for equity concerns and subgroup thresholds		1 (4)	AU
• Scenario analysis for treatment continuation rules		1 (4)	EW
• Multivariate analysis to evaluate treatment effectiveness depending on patient characteristics		1 (4)	FR

Table 1 – *continued*

	Guidelines, n (%)	Countries
• Separate models for separate subgroups	1 (4)	CA
• Equivalent data for stratified analysis as for the whole group	1 (4)	FI
• Examine whether the relative risk is constant over different baseline risk	1 (4)	SL
• Explore the possibility that differences between groups emerge by chance	1 (4)	EW

Note. Country codes according to the ISO 3166-1 Alpha-2 if applicable: Australia [22], AU; Baltics (Latvia, Estonia, and Lithuania) [40], BC*; Belgium [23], BE; Canada [24], CA; England & Wales [25], EW*; Finland [26], FI; France [27], FR; Germany [28], DE; Hungary [29], HU; Ireland [30]; IE; Israel [31], IL; New Zealand [32], NZ; Norway [33], NO; Poland [34], PL; Portugal [35], PT; Scotland [36], SL*; South Africa [37], ZA; Spain [38], ES; Sweden [39], SE; United States [41], US.
*Unofficial codes.

provide general guidance, details on the specific application of methods are provided by a minority (35%) of guidelines (Table 1) [22–28,32,36].

The German guideline advises a specific form of modeling: discrete event simulation. They argue that patient heterogeneity can be incorporated into discrete event simulation as each patient can be modeled with its unique characteristics [28]. The Canadian guideline advises stratified cost-effectiveness analysis according to the framework by Coyle et al. [1] to calculate the potential efficiency gain of subgroup policy. The Australian guideline argues that meta-regression is preferred above stratified analysis because it allows to examine multiple covariates simultaneously [22]. The French guideline advises the use of multivariate analysis to evaluate treatment effectiveness depending on patient characteristics [27]. In addition, the Australian guideline advises that the absolute treatment effect can be calculated in case of differences in baseline risk and/or treatment effect by applying the estimated relative treatment effect for the subgroups to the expected baseline risk for the subgroups [22]. The Belgium and New Zealand guidelines advise to multiply the expected baseline risk across patient subgroups by the overall relative treatment effect (assuming a constant relative treatment effect for all subgroups) [23,32].

The Australian guideline recommends performing sensitivity analysis for equity concerns that affect the cost-effectiveness and subgroup thresholds for continuous variables such as age [22]. In addition, the England & Wales guideline advises scenario analysis for treatment continuation rules [25]. These rules can be used to adjust treatment plans based on patient heterogeneity that is revealed over time (e.g., differences in treatment response). The guideline provides guidance on the specification of treatment continuation rules focusing on the feasibility, robustness, and equity of implementing these rules [25]. Finally, the England & Wales guideline advises to explore the possibility that differences between subgroup emerge by chance, especially in case numerous subgroups are reported [25].

Presenting Patient Heterogeneity

Guidance on presenting patient heterogeneity is provided by 15 guidelines (58%) [22–25,27,28,30,32,34,36–41] (Table 2). For the "Methods" section, the most common advice was to describe the definition [22–25,28,32,36,37] and justification of subgroups [22,23,25,30,32,34,36,40]. Cost-effectiveness estimates should be presented separately for each subgroup in the "Results" section according to seven guidelines (27%) [24,25,27,28,30,38,41]. Presenting the implications of subgroup policy on distributional aspects is recommended by six guidelines (23%) [22,24,27,28,30,41]. This includes highlighting unmet needs of certain disadvantaged groups. The United States guideline advises to weigh subgroup outcomes against moral values [41]. Detailed tables to present the assessment of treatment effects across subgroups are provided by the Australian guideline [22].

For the "Discussion" section, it was recommended to highlight biomarkers/diagnostic tests necessary to identify relevant subgroups [22,41], whether subgroup results lead to different conclusions than the overall trial results [22], the credibility of the claim to use subgroups [22,41], and the appropriate use of the intervention [24].

Discussion

We reviewed guidance from national pharmacoeconomic guidelines with regard to acknowledging patient heterogeneity in economic evaluations. Although the majority of guidelines considered it relevant to acknowledge patient heterogeneity, only few specified specifically which inputs of an economic evaluation are relevant for this purpose. Consistently, most guidelines provide general guidance how to acknowledge patient heterogeneity (mostly stratified analysis). Specific and in-depth guidance on applying, for instance, stratified analysis or other methods, however, was scarce and generally limited if provided. Also, guidance was "heterogeneous" between guidelines. This might reflect differences between health care systems or jurisdictions. For example, if cost-effectiveness is important for reimbursement decisions, guidelines might be more specific and directive. This can be illustrated by England and Wales, in which reimbursement decisions are based on cost-effectiveness outcomes, and who accordingly provide one of the most specific guidelines. Overall, our review revealed that the importance of acknowledging patient heterogeneity is usually recognized, while there is a lack of consensus and specific guidance on acknowledging and presenting patient heterogeneity.

One study limitation was that we excluded seven guidelines that were not written in English. Translations of guidelines from South America and Asia would be helpful to obtain a complete overview. Nevertheless, with 26 included guidelines, this review provides a comprehensive and probably representative overview of guidance on handling patient heterogeneity in economic evaluation. Also, the review was restricted to guidelines available on the ISPOR Web site. As a result, some guidelines might not be included in the review. However, when considering that a large part of the national pharmacoeconomic guidelines is published in the "gray literature," a systematic search strategy in, for instance, PubMed would most likely not lead to a

Table 2 – Overview of advice on the presentation of patient heterogeneity from guidelines (N = 26).

	Guidelines, n (%)		Countries
Total	15 (58)		AU, BC, BE, CA, EW, FR, DE, IE, NZ, PL, SL, ZA, ES, SE, US
A Present in the "Objective/Methods" section:	12 (46)		AU, BC, BE, CA, EW, DE, IE, NZ, PL, SL, ZA, SE
• Definition of subgroups		8 (31)	AU, BE, CA, EW, DE, NZ, SL, ZA
• Justification for subgroups (prespecification or biological/clinical/statistical reasoning)		8 (31)	AU, BC, BE, EW, IE, NZ, PL, SL
• Epidemiological data/number of persons for the subgroups		2 (8)	BE, SE
• How stratified analysis was undertaken, including the choice of scale on which any effect modification is defined		2 (8)	EW, SL
• Adjustments for multiple comparisons if subgroups were non-presepcified		1 (4)	AU
• Details of the statistical tests used		1 (4)	SL
• Expected differences between subgroups in methods		1 (4)	BE
• Used methods to identify the baseline data for stratified analysis		1 (4)	EW
B Present in the "Results" section:	9 (35)		AU, CA, EW, FR, DE, IE, PL, ES, US
• Cost-effectiveness information separately for each subgroup		7 (27)	CA, EW, FR, DE, IE, ES, US
• Implications for distributive aspects/equity		6 (23)	AU, CA, FR, DE, IE, US
• The impact of using the intervention for subgroups/how much the intervention is more cost-effective in the subgroups		2 (8)	DE, PL
• Subgroup results in a tornado diagram		2 (8)	CA, IE
• Cost-effectiveness acceptability curves/efficiency frontiers separately for each subgroup		1 (4)	IE
• The number of prespecified and non-prespecified stratified analysis		1 (4)	AU
• The subgroups "n (event)/N" per trial, overall trial results, treatment effect for subgroups, analysis as relative risk and risk difference both per trial and pooled		1 (4)	AU
C Present in the "Discussion" section:	3 (12)		AU, CA, US
• Discuss the claim to justify the use of subgroups (e.g., evidence or pharmacological, biological, and clinical plausibility for the variation in (cost-) effectiveness)		2 (8)	AU, US
• Discuss the biomarkers or other diagnostics (e.g., validity, reliability, and feasibility for clinical practice) necessary to identify patient subgroups		2 (8)	AU, US
• Discuss whether subgroup results lead to different conclusions than the primary overall trial results		1 (4)	AU
• Discuss the appropriate use of the intervention		1 (4)	CA

Note. Country codes according to the ISO 3166-1 Alpha-2 if applicable: Australia [21], AU; Baltics (Latvia, Estonia, and Lithuania) [20], BC*; Belgium [22], BE; Canada [23], CA; England & Wales [24], EW*; France [37], FR; Germany [26], DE; Ireland [27], IE; New Zealand [29], NZ; Poland [31], PL; Scotland [33], SL*; South Africa [34], ZA; Spain [39], ES; Sweden [35], SE; United States [36], US.
*Unofficial codes.

representative and complete overview of guidelines. Alternatively, using personal knowledge and contacts to identify national pharmacoeconomic guidelines would potentially lead to selection bias; that is, pharmacoeconomic guidelines from well-known guideline authorities (e.g., the National Institute for Health and Clinical Excellence) would be more likely to be included. In contrast, consulting the ISPOR Web site to identify national pharmacoeconomic guidelines can be regarded as a reproducible and thus systematic method to identify these guidelines and provide a representative overview of guidance. In our opinion, there is no better alternative to identify national pharmacoeconomic guidelines and consulting the ISPOR Web site can thus be regarded as the best available method for this purpose. Furthermore, there will certainly be subjectivity in our assessment of, for example, what is considered guidance and what is not. Hence, some of our evaluations may be criticized. However, by developing a data extraction sheet and organizing consensus meetings, we put all efforts to keep the assessments as systematic and objective as possible. Moreover, despite some potentially subjective judgments, this study aimed to facilitate informed discussions and advance current practice of economic evaluations. Finally, our review was restricted to

pharmcoeconomic guidelines, whereas guidelines on the clinical effectiveness/benefit assessment might provide recommendations on handling patient heterogeneity for differences in relative treatment effectiveness. This restriction is to our opinion appropriate because economic evaluations have a broader perspective; they consider consequences on the absolute scale and include additional input parameters as baseline risk, health state utility, and resource utilization. In addition, health economic researchers will probably consult and adhere to the national pharmacoeconomic guideline.

In addition to the limitations in the presented review, current literature and guidelines might sometimes be confusing concerning the handling of patient heterogeneity. The German guideline [28] uses patient heterogeneity as an argument for patient-level simulation (discrete event simulation). This argument is in our opinion incorrect. Patient-level simulation is not necessarily required to acknowledge patient heterogeneity (see, e.g., [48,49]). Subgroups can, for instance, be modeled in cohort models by letting them start in different health states [50]. Patient-level simulation is a useful alternative if this becomes too complex [9].

Although it inevitably takes time before new concepts are incorporated in guidelines, it was obvious that more clear and specific guidance would be useful. Ideally, guidelines would clearly state situations in which patient heterogeneity is considered irrelevant for decision making in their jurisdiction (e.g., using equity constraints as the guideline from England & Wales [25]). This enables researchers to focus on subgroups that are potentially useful for decision making. The framework presented by Grutters et al. [9] might be valuable to systematically explore which sources and inputs of patient heterogeneity are deemed (ir)relevant. In addition, individual preferences are a special source of patient heterogeneity. Preference subgroups can be acknowledged by using individual preferences [5,51]. However, it has been debated whether individual preferences should be incorporated in population reimbursement decisions [52–55]. Subgroups based on individual utilities may be inconsistent with the idea that societal welfare should be determined by aggregating the preferences of society [56,57]. However, as proposed by Sculpher and Gafni [58], it is possible to acknowledge diversity in the preferences of individuals while maintaining the use of utility values of the general public. Guidelines should clarify how to deal with differences in individual preferences. The guideline from England & Wales, for instance, argues against subgroups solely based on individual utilities (Table 1).

Most guidelines consider patient heterogeneity that is known at the start of treatment. In addition, the England & Wales guideline provides guidance to construct treatment continuation rules based on patient heterogeneity revealed over time [25]. Treatment continuation rules (e.g., based on treatment response) can be used to adjust treatment plans after treatment start. However, it might be complex to attain feasible treatment continuation rules and inform actual reimbursement decisions based on patient heterogeneity revealed over time. Therefore, guidelines should clarify, as the England & Wales guideline [25], how patient heterogeneity revealed over time should be handled.

It is recommended that guidelines be as specific as possible when stratified analysis should be undertaken (e.g., what justification is required and in which circumstances post hoc analyses are allowed). This potentially prevents that subgroups are analyzed only if average cost-effectiveness is hard to show. In addition, the possibility of false positives due to random noise in data might caution researchers or policymakers to use subgroups in their analysis or decision making [9]. These fears, however, are mainly from an epidemiological perspective [3]. From a health economic perspective, the statistical significance of subgroups is irrelevant [59]; rather, its value for reimbursement decisions is relevant. Certainly, this does not mean that uncertainty is irrelevant [59,60] and data dredging should always be avoided. The role of stratified analysis in economic evaluations, however, should in our opinion be considered on the basis of its value for policy purposes (i.e., the health benefits forgone if subgroups are neglected), rather than from an epidemiological perspective [61].

The finding that none of the guidelines provided specific guidance how to select influential subgroups and determine subgroup thresholds or the optimal number of subgroups for continuous variables (e.g., to determine age groups) might reflect that there is no consensus on this topic. Thus, the selection of patient subgroups, particularly in case multiple (continuous) variables are considered simultaneously, may require further methodological research, as currently performed by Saramago [62] and Espinoza et al. [63] among others. Nevertheless, efforts have been made in this direction. Willan et al. [61] demonstrated that regression techniques can be used within the net benefit framework to explore and select statistically significant patient characteristics to define subgroups [64]. Furthermore, Basu and Meltzer [5] proposed a framework to estimate the expected value of individualized care. By selecting potentially influential variables based on the parameter-specific value of individualized care, this framework could be an alternative to the regression technique described above [5,65]. The selected variables can subsequently be used in stratified analyses by estimating the benefits of providing different treatments to different subgroups and hence calculating the potential value of subgroup policy [1]. This would give decision makers the opportunity to judge when the costs of equity constraints are too high [66]. In decision analytic modeling, stratified analyses can be performed by using different input values for different subgroups. This can be implemented by linking input parameters to patient characteristics or by adding health states and letting different subgroups start out in different health states [4,6,9,50].

In addition, it might be useful to provide guidance on what should be presented to support potential reimbursement decisions based on subgroup outcomes. This includes, for instance, to describe and justify subgroups, provide guidance on specific tables/figures, and highlight issues as the appropriate use of the intervention and the feasibility of subgroup policy. These recommendations require a high level of prescription in guidelines, while many are currently not this directive. It is open to debate whether decision makers wish to have such prescriptive guidelines, or prefer to leave this to the integrity of researchers. In our opinion, decision makers should clearly state which results are needed for their appraisal and how these results should be achieved in the assessment, in order to support uniformity. Taking into account the differences between jurisdictions (e.g., in terms of legislation and normative judgments), it was deemed impossible to formulate guidance that would be appropriate for all national pharmacoeconomic guidelines worldwide. Therefore, we present a checklist in Table 3 to assist national guideline authorities to formulate comprehensive recommendations with regards to acknowledging patient heterogeneity in economic evaluations on the topics identified in this review. Obviously, researchers are allowed to deviate from guideline recommendations if appropriately justified. However, especially when considering a normative subject where subgroups are potentially included or excluded from treatment reimbursement, guidelines should in our opinion be specific and directive.

In conclusion, the majority of national pharmacoeconomic guidelines provide guidance on acknowledging patient heterogeneity in economic evaluations. However, because specific guidance is often lacking, its usefulness is limited. This may reflect that the importance of acknowledging patient heterogeneity is usually recognized while there is a lack of consensus on specific requirements and methodology to acknowledge and present patient heterogeneity in economic evaluations. We

Table 3 – Checklist to formulate guidance on acknowledging patient heterogeneity in economic evaluation.

Acknowledgment of patient heterogeneity

1 In economic evaluations, patient heterogeneity
- ☐ Should not be reflected
- ☐ Should be reflected

2 When acknowledging patient heterogeneity, the following inputs of an economic evaluation should be considered*:
- ☐ Baseline risk
- ☐ Relative treatment effect
- ☐ Health state utility
- ☐ Resource utilization

3 The following sources of patient heterogeneity should be considered*:
- ☐ Demographics
- ☐ Preferences
- ☐ Clinical characteristics

Methodology to acknowledge patient heterogeneity

4 In order to analyze different sources of patient heterogeneity*,
- ☐ No justification is required
- ☐ This should be justified on the basis of biological plausibility
- ☐ This should be justified on the basis of (pre)clinical evidence/ pharmacokinetics
- ☐ This should be justified on the basis of statistical plausibility
- ☐ This should be justified on the basis of …

5 Subgroups that are a priori not considered relevant for decision making are those based solely on the following sources of patient heterogeneity:
- ☐ No subgroups are a priori considered irrelevant
- ☐ Subgroups based on the following sources are a priori considered irrelevant: …

6 Patient heterogeneity should be explored on the basis of
- ☐ Prespecified subgroups and post hoc analysis should be avoided
- ☐ Prespecified subgroups and post hoc analysis should be used only to generate hypotheses or to …
- ☐ Either post hoc analysis or prespecified subgroups

7 The following methods are suggested to analyze patient heterogeneity*:
- ☐ Stratified analysis
- ☐ Decision analytic modeling
- ☐ Sensitivity or scenario analysis
- ☐ Expected value of individualized care
- ☐ Regression analysis
- ☐ …

8 These methods should be applied in order to*
- ☐ Incorporate and analyze sources of patient heterogeneity if …
- ☐ Incorporate and analyze variability in baseline risk and/or treatment effect through …
- ☐ Determine subgroup thresholds and the number of subgroups in case of continuous variables through …
- ☐ Reflect the precision of subgroup estimates
- ☐ Handle patient heterogeneity revealed over time
- ☐ …

Presenting patient heterogeneity

9 To support subgroup policymaking, the following information should be presented*:
- ☐ Clear definition and justification of subgroups
- ☐ Details on data used to produce subgroup estimates
- ☐ Details on statistical analyses
- ☐ Stratified cost-effectiveness outcomes
- ☐ Tornado diagram
- ☐ Separate cost-effectiveness acceptability curves
- ☐ Implications for distributive aspects/equity
- ☐ Validity, reliability, and feasibility of biomarkers of diagnostics necessary to identify subgroups
- ☐ Appropriate use of the intervention

advise the further development of national pharmacoeconomic guidelines to provide specific guidance in each of the categories: the identification of patient heterogeneity, methods to acknowledge patient heterogeneity, and presenting the results when acknowledging patient heterogeneity. This could facilitate the systematic and transparent handling of patient heterogeneity in economic evaluations worldwide.

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